

### REMARKS

Reconsideration of this application, as amended, is respectfully requested. The Applicants wish to draw the Examiner's attention to the applicants' related co-pending applications and issued patents (see Appendix A) directed to nanoparticles and methods of preparation and use thereof.

The Applicants note that the Examiner did not return the executed PTO 1449 form for the 6<sup>th</sup> Supp. IDS that was hand-delivered to the Examiner on September 9, 2002. Subsequent to the issuance of this Office action, the Applicants had filed a 7<sup>th</sup> Supp. IDS. Attached copies of PTO stamped post-cards show that the Patent Office did receive both IDSs, PTO-1449 forms and cited references. The Applicants request that the Examiner fully execute the PTO 1449 forms for the 6<sup>th</sup> and 7<sup>th</sup> Supp. IDSs and return a copy of the executed PTO 1449 forms to the undersigned representative. Copies of the 6<sup>th</sup> and 7<sup>th</sup> Supplemental IDSs and associated PTO 1449 forms are attached. The Examiner is requested to contact the undersigned representative if the Examiner would like to have another copy of the references.

The specification has been amended to update the priority claim. No new matter has been added to the application as a result of this amendment.

Claims 433-480 were pending in this application. Claims 437-480 were cancelled and new claims 481-556 were added to further clarify the invention. The new claims are fully supported in the cancelled claims, and thus do not constitute new matter. The new claims are supported, for example, by claims 190-265 and 437-480 and specification on page 21, line 3 to page 22, line 22; page 77, line 1 to page 80, line 27; and page 90, line 8 to page 93, line 24. Thus, the new claims do not constitute new matter. Claims 433-436 and 481-556 are now pending in this application.

Turning to the office action, claims 433-480 stand rejected under 35 U.S.C. section 102(e) as being anticipated by, or in the alternative, under 35 USC section 103(a) as being obvious over Yguerabide (U.S. Patent No. 6,214,560) ("Yguerabide"). The Applicants respectfully traverse this rejection.

The Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983).

Likewise, the Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the

claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). Contrary to the Examiner's position, Yguerabide does not teach or suggest what the Applicants have done.

Specifically, the Examiner alleged that Yguerabide taught detection and measurement of one or more analytes in a sample using particles of specific composition and size using light scattering. The discussion is found starting in col. 82, line 35, of Yguerabide. Col. 83 provides further discussion regarding particle size and particle binding to a surface. Cols. 77-80 relate to particles and their preparation. Col. 110 (Example 32) relates to a nucleic acid labeled particle but does not provide or suggest any process for preparing conjugates as presently claimed. Moreover, Yguerabide does not teach or suggest any particle surface density. Indeed, surface density cannot be calculated since Yguerabide does not provide any DNA concentration. Furthermore, there is no discussion or suggestion anywhere in Yguerabide of a nanoparticle having any recognition and/or diluent oligonucleotides. Nanoparticle-oligonucleotide conjugates prepared by recited process exhibit melting (dehybridization) profiles that are extremely narrow compared to the profiles obtained using the same oligonucleotides not attached to nanoparticles, and exhibit extraordinary selectivity (detection as little as a single base difference) and sensitivity (detecting as little as 10 femtomoles of nucleic acid without amplification) have been obtained using these conjugates in such assays (see particularly Examples 5, 7 and 19) of the present application. These conjugates are surprisingly more stable compared to conjugates made without the recited steps (see, e.g., Example 3 of the present application). The claims recite limitations that are neither taught, made obvious, or suggested by Yguerabide.

Thus, the Applicant respectfully submits that Yguerabide cannot be applied to support section 102(e) and/or section 103(a) rejections of claims 433-436 and 481-556.

Claims 439-443 also stand rejected under 35 U.S.C. section 112, second paragraph, for alleged indefiniteness. The Examiner alleged that the claim 439 (now cancelled) had improperly depended from a cancelled claim and thus the aforementioned claims are indefinite. The Applicant believes that this rejection is now moot in light of the cancellation and replacement of the aforementioned claims with the new claims.

Finally, claims 444-461 (now claims 492-533) stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 243-265 of Applicant's copending application 09/974,007 (the '007 application). The Applicant respectfully traverses this rejection. Claims 444-461 are directed to a general method of preparing nanoparticle

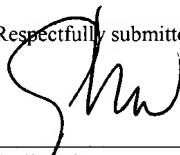
conjugates (e.g., see claim 444) while the composition claims of the '007 application (e.g. 243) are directed to nanoparticle conjugates. In this case, comparison of composition claims of the '007 application does not suggest the steps of a method for preparing conjugates as presently claimed. Accordingly, the Applicant respectfully submit that the obviousness-type double patenting rejection of the method claims 444-461(now claims 492-533) in light of the composition claims of the '007 application is improper and should be withdrawn. The Applicants also note that the claims in the '007 application have not been allowed. Thus, at the very least, the Applicants request that the provisional rejection of the claims be held in abeyance until the claims in this application or in the '007 application are found to be allowable.

In conclusion, the Applicants respectfully submit that the claims in this application are in allowable condition and request a Notice to this effect.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes that this would be helpful in expediting the prosecution of this application.

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Respectfully submitted,



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## APPENDIX A

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
00-653-A	U.S. 09/927,777 Filed 8/10/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton, Garamella, Li, Park/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFORE	PENDING
00-713-B1	09/923,625 Filed 8/7/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFOR	PENDING
00-713-C	09/344,667, filed 6/25/99	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFORE	U.S. Patent No. 6,361,944, issued 3/26/02
00-713-I	U.S.S.N 09/603,830 Filed 6/26/00	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton; NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFOR	U.S. Patent No. 6,506,564, issued 1/14/03
00-713-I-1	09/961,949 9/20/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton;	U.S. Patent No. 6,582,921, issued June 24, 2003

<b>ATTY Case No.</b>	<b>Serial No./ Filing Date</b>	<b>Inventors/Title</b>	<b>Status</b>
		NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERETO AND USES THEREFOR	
<b>00-713-I-2</b>	09/957,318 9/20/01	See 00-713-I-1	PENDING
<b>00-713-I-3</b>	09/957,313 9/20/01	See 00-713-I-1	ALLOWED
<b>00-713-I-4</b>	09/966,491 9/28/01	See 00-713-I-1	U.S. Patent No. 6,610,491
<b>00-713-I-5</b>	09/966,312 9/28/01	See 00-713-I-1	ALLOWED
<b>00-713-I-6</b>	09/967,409 9/28/01	See 00-713-I-1	PENDING
<b>00-713-I-7</b>	09/974,500 10/10/01	See 00-713-I-1	ALLOWED
<b>00-713-I-8</b>	09/974,007 10/10/01	See 00-713-I-1	PENDING
<b>00-713-I-9</b>	09/973,638 10/10/01	See 00-713-I-1	PENDING
<b>00-713-I-10</b>	09/973,788 10/10/01	See 00-713-I-1	ALLOWED
<b>00-713-I-11</b>	09/975,062 10/11/01	See 00-713-I-1	ALLOWED
<b>00-713-I-12</b>	09/975,376 10/11/01	See 00-713-I-1	PENDING
<b>00-713-I-13</b>	09/975,384 10/11/01	See 00-713-I-1	PENDING
<b>00-713-I-14</b>	09/975,498 10/11/01	See 00-713-I-1	ALLOWED

<b>ATTY Case No.</b>	<b>Serial No./ Filing Date</b>	<b>Inventors/Title</b>	<b>Status</b>
00-713-I-15	09/975,059 11/11/01	See 00-713-I-1	PENDING
00-713-I-16	09/976,601 10/12/01	See 00-713-I-1	PENDING
00-713-I-17	09/976,968 10/12/01	See 00-713-I-1	PENDING
00-713-I-18	09/976,971 10/12/01	See 00-713-I-1	ALLOWED
00-713-I-19	09/976,863 10/12/01	See 00-713-I-1	PENDING
00-713-I-20	09/976,577 10/12/01	See 00-713-I-1	ALLOWED
00-713-I-21	09/976,618 10/12/01	See 00-713-I-1	PENDING
00-713-I-22	09/981,344 10/15/01	See 00-713-I-1	PENDING
00-713-I-23	09/976,900 10/12/01	See 00-713-I-1	PENDING
00-713-I-24	09/976,617 10/12/01	See 00-713-I-1	PENDING
00-713-I-25	09/976,378 10/12/01	See 00-713-I-1	PENDING
00-713-i-26	10/410,324 04/10/03	See 00-713-I-1	PENDING
00-713-L	U.S.S.N. 09/693,005 Filed 10/20/00	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERE TO AND	U.S. Patent No. 6,495,324, issued 12/17/02

<b>ATTY Case No.</b>	<b>Serial No./ Filing Date</b>	<b>Inventors/Title</b>	<b>Status</b>
		USES THEREFORE	
<b>00-713-M</b>	U.S.S.N. 09/693,352 Filed 10/20/00	Mirkin, Letsinger, Mucic, Storhoff, Elghanian/ NANOPARTICLES HAVING OLIGONUCLEOTI DES ATTACHED THERE TO AND USES THEREFORE	U.S. Patent No. 6,417,340, issued 7/9/02
<b>00-714-G</b>	U.S. 09/830,620 Filed 8/15/01	Mirkin, Nguyen/ NANOPARTICLES WITH POLYMER SHELLS	PENDING
<b>00-715-A</b>	U.S. 09/760,500 Filed 1/12/01	Mirkin, Letsinger, Mucic, Storhoff, Elghanian, Taton; Garamella, Li/ METHOD OF ATTACHING OLIGONUCLEOTI DES TO NANOPARTICLES AND PRODUCTS PRODUCED THEREBY	ALLOWED
<b>00-1085-A</b>	U.S.S.N. 09/820,279 Filed 3/28/01	Mirkin, Letsinger, etc./ METHOD AND MATERIALS FOR ASSAYING BIOLOGICAL MATERIALS	ALLOWED
<b>00-1086-A</b>	U.S. 09/903,461 Filed 7/11/01	Letsinger, Garamella/ METHOD OF DETECTION BY ENHANCEMENT OF SILVER STAINING	U.S. Patent No. 6,602,669, Filed 8/5/03
<b>01-565-A</b>	USSN 10/125,194 Filed 4/18/02	Mirkin, Nguyen, Watson, Park/ OLIGONUCLEOTI DE-MODIFIED ROMP POLYMERS AND CO-	PENDING

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
		POLYMERS	
01-599-A	U.S.S.N. 10/291,291 Filed 11/08/02	Storhoff/NOVEL THIOL-BASED METHOD FOR ATTACHING OLIGONUCLEOTI DES TO NANOPARTICLES	PENDING
01-661-A	U.S.S.N. 10/034,451 Filed 12/28/01	Mirkin, Cao, Jin/ DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	PENDING
01-661-C	U.S.S.N. 10/153,483 Filed 5/22/02	Mirkin, Cao, Jin/ DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	PENDING
01-661-E	U.S.S.N. 10/397,579 3/26/03	Mirkin, Cao, Jin/ DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	PENDING
01-1565-A	U.S.S.N. 10/266,983 Filed 10/08/02	Park, Taton, Mirkin/ARRAY- BASED ELECTRICAL DETECTION OF DNA USING NANOPARTICLE PROBES	PENDING
01-1705-A	U.S.S.N. 10/108,211 Filed 3/27/02	Nam, Park, Mirkin/BIO- BARCODES BASED ON OLIGONUCLEOTI DE-MODIFIED NANOPARTICLES	PENDING
02-338-B	USSN 10/172,428 Filed 6/14/02	Cao, Jin, Nam, Mirkin/MULTIHA NNEL DETECTION USING NANOPARTICLE PROBES WITH	PENDING



ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
		RAMAN SPECTROSCOPIC FINGERPRINTS	
02-338-C	10/431,341 5/7/03	Cao, Jin, Nam, Mirkin/MULTICHA NNEL DETECTION USING NANOPARTICLE PROBES WITH RAMAN SPECTROSCOPIC FINGERPRINTS	PENDING